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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,139	01/10/2006	Herve Rolland	SERVIER 479 PCT	6115

25666 7590 04/14/2009

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EXAMINER	
RICCI, CRAIG D	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
04/14/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,139	ROLLAND ET AL.	
	Examiner	Art Unit	
	CRAIG RICCI	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/10/2006, 7/13/2006 and 1/15/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. The amendments filed 01/15/2009 were entered.

Response to Arguments

2. Applicants' arguments, filed 01/15/2009, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Priority

3. Acknowledgment is made of Applicant's claim for foreign priority pursuant to 35 U.S.C. 119(a) and 365(b) based on a prior application filed in France on 07/17/2003. The certified copy has been filed in parent Application No. PCT/FR04/01867, filed on 07/16/2004 and a certified English translation has been provided. Accordingly, Applicant's claim to priority has been perfected.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. **Claims 7-12 rejected under 35 U.S.C. 103(a) as being unpatentable over *Merkus* (US 5,756,483; cited in a previous Action) in view of *Deleu et al* (Clin Pharmacokinet 41(4):261-309, 2002; cited in a previous Action)**.

7. As discussed in a previous Action mailed on 07/14/2008, instant claim 7 is drawn to a pharmaceutical composition in the form of an aqueous solution or powder for nasal administration of piribedil, comprising piribedil, optionally a cyclodextrin, and one or more pharmaceutically acceptable excipients. More specifically, the piribedil is in the form of the base (claim 8) and the cyclodextrin is a partially methylated β-cyclodextrin (claim 9) wherein the degree of substitution by methyl groups is about 1.7 (claim 10).

8. *Merkus* teaches pharmaceutical compositions for intranasal administration of apomorphine, which is a "very potent dopamine agonist... used as an adjunctive medication in the treatment of Parkinson's disease" (Column 3, Lines 53-56). More specifically, *Merkus* teaches apomorphine in the form of the base (Column 5, Example 1A, Line 28) and *Merkus* also teaches apomorphine in combination with a cyclodextrin,

preferably “methylated β-cyclodextrin with a degree of CH_3-substitution between 0.5 and 3.0, more preferably between 1.7 and 2.1” (Column 4, Lines 26-31). Additionally, *Merkus* teaches that “many other excipients, known in the pharmaceutical literature, can be added" to the disclosed composition (Column 5, Lines 7-9) and that the composition can be administered “as a nasal spray... or powder" (Column 4, Lines 36-38). However, *Merkus* does not teach piribedil. Thus, although *Merkus* teaches each of the elements of instant claims 7-10, *Merkus* does not teach a composition comprising piribedil. Rather, the composition that *Merkus* teaches comprises apomorphine. Accordingly, the only difference between claims 7-10 of the instant application and *Merkus* is that Applicant has replaced apomorphine in the composition taught by *Merkus* with pirebedil.

9. *Deleu et al* teaches that apomorphine and piribedil are both dopamine agonists with similar mechanisms of action, similar effects and similar uses such as the treatment of Parkinson's disease (entire document). In the case of Parkinson’s disease, *Deleu et al* specifically teach that “no single best treatment exists for an individual patient with Parkinson’s disease. Particularly in the advanced stage of the disease, treatment should be individually tailored” (abstract).

10. Accordingly, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to replace apomorphine (as taught by *Merkus*) with piribedil as recited by the instant claims. One of ordinary skill in the art would have been motivated to use, in place of apomorphine in the invention taught by *Merkus* as useful in the treatment of Parkinson’s disease, other dopamine agonists useful in the treatment of Parkinson’s disease, such as piribedil. Since it would have

been obvious to substitute apomorphine with piribedil in view of *Deleu et al*, and since *Merkus* teaches all the other limitations of instant claims 7-10 as discussed above, claims 7-10 are obvious.

11. Applicant, however, contends that *Deleu et al* does not teach the equivalence of apomorphine and piribedil and the disclosure that "no single best treatment exists for an individual patient with Parkinson's disease. Particularly in the advanced stage of the disease, treatment should be individually tailored" represents nothing more than an invitation to experiment with respect to the use of various substances for the treatment of Parkinson's disease (Applicant Argument, Pages 5-6). This argument is not found persuasive. As stated by the Court in *KSR International Co., v. Teleflex Inc.*, 127 US 1727 (2007), "when a patent 'simply arranges old elements with each performing the same function it had been known to perform' and yields no more than one would expect from such an arrangement, the combination is obvious" (quoting *Sakraida v. AG Pro, Inc.*, 425 US 273 (1976)). In the instant case, *Deleu et al* teach that apomorphine and piribedil are both dopamine agonists useful for the treatment of Parkinson's disease. The simple substitution of one known element (i.e., one known dopamine agonist - apomorphine) for another (i.e., another known dopamine agonist - piribedil) to obtain predictable results is *prima facie* obvious. Additionally, since *Deleu et al* specifically state "no single best treatment exists for an individual… treatment should be individually tailored", the skilled artisan would have been motivated to consider different dopamine agonists (other than simply apomorphine as taught by *Merkus*) for the treatment of Parkinson's disease. As stated by the Court in *KSR International Co., v. Teleflex Inc.*,

127 US 1727 (2007), "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her grasp. If this leads to the anticipated success, it is likely the product not of innovation, but of ordinary skill and common sense." In the instant case, there is clearly a need to treat Parkinson's disease and a recognition in the art of a problem - namely that "no single best treatment exists for an individual… treatment should be individually tailored". Since *Deleu et al* disclose a finite number of identified dopamine agonists useful in the treatment of Parkinson's disease, pursuing the known options in an effort to provide individually tailored treatment would have been obvious to a person of ordinary skill.

12. Applicant further argues that piribedil and apomorphine are structurally distinct molecules (noting that *Deleu et al* disclose that piribedil is a non-ergoline dopamine agonist whereas apomorphine is an aporphine dopamine agonist) and that one skilled in the art would recognize that piribedil and apomorphine would possess different pharmacological/pharmacokinetic profiles based on these structural differences (Applicant Argument, Pages 5-6). Indeed, Applicant is correct that most dopamine agonists have their specific pharmacological profile and pharmacokinetic properties, and the skilled artisan would similarly expect piribedil and apomorphine to each posses a specific pharmacological profile and pharmacokinetic properties. Although Applicant's argument as to this point is not clear, it is possible that Applicant is arguing that, since piribedil and apomorphine would possess different pharmacological/pharmacokinetic profiles, one would not reasonably expect their simple substitution **to provide**

predictable results. If so, this argument is not found persuasive. First, it is noted that *Deleu et al* explicitly state that piribedil has a favorable therapeutic profile (Page 288, Column 2, First Paragraph). And second, discussing ergot-derived dopamine agonists, *Deleu et al* states that "the pharmacokinetic properties of ergot-derived dopamine agonists vary substantially among each other. Despite this, their clinical effects and adverse effects are broadly similar" (Page 300, Column 1, Second Paragraph). Thus, for both of these reasons, even though the compounds may be expected to possess distinct pharmacological/pharmacokinetic profiles, the skilled artisan would have reasonably expected the substitution of apomorphine with piribedil to yield predictable results. Alternatively, Applicant's argument as to the distinct pharmacological/pharmacokinetic profiles may be specifically directed to instant claims 11-12, which are drawn to the amount of piribedil in the composition. As such, it is possible that Applicant is arguing that, since piribedil and apomorphine would be expected to have different pharmacological/pharmacokinetic profiles, the skilled artisan would be required to modify the amount of piribedil used in a composition from the amount of apomorphine that is taught by *Merkus* in order to formulate a composition providing predictable results. If so, Applicant is directed to the previous Action where it was stated that as drafted, claim 11 defines the amount of piribedil and cyclodextrin as percent weight per volume, and an aqueous solution of 10 ml is not read as limiting. Alternatively, claim 11 can be read to define the amount of piribedil and cyclodextrin as a ratio of each other, and an aqueous solution of 10 ml is not read as limiting. Furthermore, as drafted, claim 12 is read to define the amount of piribedil and

cyclodextrin as a ratio of each other and the absolute values are not a limitation. Accordingly, this argument is not found persuasive since the skilled artisan would have maintained the same ratio of dopamine agonist:cyclodextrin (a known permeation promoter) regardless of the dopamine agonist employed. As such, the rejection of claims 11 and 12 in the previous Action (which is included below) is also maintained

13. Claim 11 defines a solution wherein the amount of piribedil is from 0.1 to 5% w/v for an amount of cyclodextrin of from 0.75 to 37.5% w/v. *Merkus* teaches a composition wherein the amount of apomorphine is 1% w/v and cyclodextrin is 4% w/v (Column 5, Example 3, Lines 65-67). Alternatively, claim 11 can be read to define the amount of piribedil and cyclodextrin as a ratio of each other, and an aqueous solution of 10 ml is not read as limiting. In this case, claim 11 defines a solution wherein the ratio of piribedil to cyclodextrin is from 1:0.15 to 1:375. The ratio of piribedil to cyclodextrin taught by *Merkus* is 1:4 (Column 5, Example 3, Lines 65-67). As stated in MPEP 2131.03, a specific example in the prior art which is within a claimed range anticipates the range. Since it would have been obvious to substitute apomorphine with piribedil in view of *Deleu et al* as discussed above, and since *Merkus* anticipates the range of instant claim 11, claim 11 is obvious.

14. Instant claim 12 is drawn to the composition of claim 7 wherein "the composition is in powder form and amount of pirbedil is from 0.1 mg to 20 mg for an amount of cyclodextrin of from 7.5 to 75 mg" (claim 12). As drafted, claim 12 is read to define the amount of piribedil and cyclodextrin as a ratio of each other and the absolute values are not a limitation. Thus, claim 12 defines a composition wherein the ratio of piribedil to

cyclodextrin is from 1:0.375 to 1:750. As taught by *Merkus*, for a 10 mg powder formulation, the amount of apomorphine is 1 mg and the amount of cyclodextrin is 5 mg (Column 5, Example 1A, lines 27-31). Accordingly, *Merkus* teaches a composition wherein the ratio of piribedil to cyclodextrin is 1:5 (Column 5, Example 1A, lines 27-31). As stated in MPEP 2131.03, a specific example in the prior art which is within a claimed range anticipates the range. Since it would have been obvious to substitute apomorphine with piribedil in view of *Deleu et al* as discussed above, and since *Merkus* anticipates the range of instant claim 12, claim 12 is obvious.

Conclusion

No new ground(s) of rejection are presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CRAIG RICCI whose telephone number is (571) 270-

5864. The examiner can normally be reached on Monday through Thursday, and every other Friday, 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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